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# Opposing Metabolic Effects of Growth Hormone and Insulin-like Growth Factor I: Review and Clinical Implications

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## Abstract

The growth hormone (GH) and insulin-like growth factor I (IGF-I) axis is fundamental to growth and metabolism, yet the distinct and often opposing metabolic actions of these 2 hormones are not always appreciated in clinical practice, necessitating a comprehensive synthesis of current evidence. Understanding this dichotomy is essential for optimizing therapeutic strategies in endocrine and metabolic disorders, where hormone modulation carries both benefits and risks. This review starts by examining the molecular mechanisms of GH and IGF-I signaling, including receptor activation and downstream pathways such as Janus kinase 2- signal transducer and activator of transcription (JAK2-STAT) and Phosphoinositide 3-kinase-protein kinase B (PI3K-AKT). It then explores the physiological roles of each hormone, highlighting GH's direct catabolic effects on glucose and lipid metabolism and IGF-I's insulin-sensitizing and anabolic properties. The tissue-specific actions of GH and IGF-I in the liver, adipose tissue, skeletal muscle, and pancreas are discussed to illustrate their divergent metabolic targeting. The integrated regulation of the GH-IGF-I axis by factors such as exercise, nutrition, and feedback inhibition is also addressed. Finally, the review overviews evidence from recent clinical studies examining GH and IGF-I in conditions including type 2 diabetes, GH deficiency, and acromegaly, and considers the therapeutic implications of their opposing effects. Future research should focus on the precise molecular determinants of tissue-specific hormone sensitivity to enable more targeted interventions. Combination therapies and personalized medicine approaches, guided by genetic and metabolic profiling, hold particular promise for harnessing the beneficial effects of GH and IGF-I while mitigating their respective adverse metabolic consequences.

**Keywords:** Diabetes mellitus, Growth hormone, Insulin resistance, Insulin-like growth factor I, Metabolic syndrome, Type 2 diabetes

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## Introduction

GH and IGF-I are central components of the endocrine system that regulate growth and metabolism [1-10]. GH, secreted by the anterior pituitary, exerts its effects both directly and indirectly through the stimulation of IGF-I production primarily in the liver and other tissues [11]. IGF-I, in turn, mediates many of the anabolic and growth-promoting actions attributed to GH, functioning as a key effector molecule in the GH/IGF-I axis [11]. Despite their interconnected roles, GH and IGF-I exhibit distinct and sometimes opposing effects on various metabolic processes, a phenomenon that has been recognized and studied extensively over the years [11]. The complex interplay between these hormones is fundamental to understanding normal physiology and the pathophysiology of metabolic disorders, making their study a cornerstone of endocrinology research [12].

The metabolic effects of GH and IGF-I are of significant clinical interest due to their implications in health and disease. GH influences glucose, lipid, and protein metabolism, often promoting lipolysis and gluconeogenesis, which can lead to insulin resistance if dysregulated [11]. Conversely, IGF-I generally exerts insulin-like effects, promoting glucose uptake and anabolic processes [13]. Recognizing the opposing nature of these hormones' actions is crucial for developing targeted therapies for conditions such as GH deficiency, acromegaly, diabetes, and metabolic syndrome [2]. Furthermore, understanding their divergent effects aids clinicians in balancing therapeutic benefits against potential risks, such as hyperglycemia or dyslipidemia, associated with hormone supplementation or suppression [14]. As research advances, elucidating these mechanisms remains vital for optimizing treatment strategies and improving patient outcomes [11].

This review aims to overview current literature on the opposing metabolic effects of GH and IGF-I, highlighting their distinct mechanisms of action and physiological roles. By comparing their impacts on key metabolic pathways—particularly glucose, lipid, and protein metabolism—the review aims to clarify how these hormones influence overall metabolic homeostasis. Additionally, it discusses the clinical implications of their divergent actions, including considerations for managing metabolic disorders and hormone-related

diseases. Ultimately, the review endeavors to provide a comprehensive understanding that can inform future research directions and therapeutic approaches targeting the GH/IGF-I axis [11].

## Molecular Mechanisms of GH and IGF-I Signaling

The molecular mechanisms of GH and IGF-I signaling are complex and involve multiple pathways that regulate growth, metabolism, and cellular functions [15-21]. GH and IGF-I interact through their respective receptors, triggering a cascade of intracellular events that influence gene expression and cellular behavior [22-30]. These pathways are crucial for understanding various physiological processes and potential therapeutic targets for related disorders.

GH binds to the GH receptor, a member of the cytokine receptor superfamily, which activates JAK2. This activation leads to the phosphorylation of STAT5, which is crucial for mediating GH's effects, including the transcription of the IGF-I gene in the liver and other tissues [20, 31, 32]. IGF-I binds to the IGF-I receptor, a tyrosine kinase receptor, initiating signaling pathways such as PI3K/AKT and mitogen-activated protein kinase (MAPK), which promote cell proliferation and survival [33, 34]. GH and IGF-I signaling pathways exhibit cross-talk, where GH can enhance IGF-I receptor signaling, and vice versa. This interaction is evident in pancreatic β-cells, where GH and IGF-I synergistically activate STAT5 and AKT pathways, enhancing cell proliferation and survival [33, 34].

The GH-IGF-I axis is essential for postnatal growth, bone development, and metabolic regulation. Dysregulation can lead to conditions such as gigantism, acromegaly, or GH deficiencies [20, 35]. Reduced GH and IGF-I levels are associated with aging-related conditions like sarcopenia and osteoporosis. Impaired signaling due to receptor or post-receptor defects contributes to these age-related declines [35]. While GH and IGF-I are vital for growth and repair, their signaling pathways have been implicated in cancer development and reduced lifespan in experimental models, highlighting the need for a balanced understanding of their roles [36].

GH influences gene expression by activating STAT5b, which binds to DNA and regulates genes like IGF-I. This regulation involves epigenetic changes and interactions with other transcription factors [31, 32]. GH-induced IGF-I expression involves JAK-STAT pathways and additional tyrosine phosphorylation mechanisms, particularly involving the C-terminal region of the GHR, which are crucial for full gene activation [37].

## Physiological Roles of GH

GH exerts its physiological effects primarily through direct interactions with target tissues and indirectly via stimulation of IGF-I production, predominantly in the liver [38-40]. GH binds to specific receptors on cell surfaces, activating intracellular signaling pathways such as the JAK2-STAT pathway, which modulates gene expression related to growth and metabolism [11]. Additionally, GH influences lipolysis, protein synthesis, and glucose homeostasis through its direct actions on adipose tissue, muscle, and the liver [11]. The secretion of GH is pulsatile and regulated by hypothalamic hormones, including GH-releasing hormone and somatostatin, which finely tune its physiological effects [41]. The complex interplay between GH and IGF-I pathways underpins the diverse biological functions of GH, with IGF-I mediating many of the growth-promoting effects while also contributing to metabolic regulation [11].

GH plays a pivotal role in regulating intermediary metabolism, exhibiting predominantly catabolic effects on carbohydrate metabolism and anabolic effects on lipid and protein metabolism [11]. It stimulates lipolysis in adipose tissue, leading to increased free fatty acid mobilization and utilization, which provides alternative energy sources during fasting or energy deficits [13]. Conversely, GH antagonizes insulin action, resulting in decreased glucose uptake in peripheral tissues and promoting gluconeogenesis in the liver, thereby elevating blood glucose levels [11]. This antagonistic effect on glucose metabolism is a key feature of GH's metabolic profile and has significant implications for glucose homeostasis and insulin sensitivity [11]. In terms of protein metabolism, GH promotes amino acid uptake and protein synthesis in muscle tissues, supporting growth and tissue repair [12]. Overall, GH's metabolic actions are complex and context-dependent, balancing energy mobilization with anabolic processes to support growth and metabolic homeostasis [11].

Clinically, GH therapy is employed to treat GH deficiency, certain metabolic disorders, and conditions characterized by impaired growth [2]. Its ability to stimulate growth and modulate metabolism makes it a valuable therapeutic agent in pediatric and adult populations [42]. In GH deficiency, exogenous GH administration restores normal growth patterns and improves body composition [43]. However, due to its opposing effects on glucose metabolism, GH therapy requires careful monitoring to prevent adverse effects such as insulin resistance or hyperglycemia [11]. In adults, GH therapy can improve muscle mass, reduce adiposity, and enhance quality of life, but clinicians must weigh these benefits against potential risks, including metabolic disturbances and cardiovascular effects [14]. Understanding the physiological mechanisms and metabolic effects of GH is essential for optimizing its clinical use and minimizing adverse outcomes (Table 1) [11].

## Tissue-specific Actions and Metabolic Targeting

GH and IGF-I are critical components of the somatotropic axis, exerting distinct and sometimes opposing effects on various tissues, including the liver, adipose tissue, skeletal muscle, and pancreas [44-53]. These hormones play essential roles in growth, metabolism,

**Table 1:** Summary of GH physiological roles and clinical implications.

| Aspect | Key points |
|---|---|
| Primary mechanisms | • Direct action via GH receptor binding (JAK2-STAT pathway)<br>• Indirect action via stimulation of hepatic IGF-I production<br>• Pulsatile secretion regulated by growth hormone-releasing hormone and somatostatin |
| Carbohydrate metabolism | • Antagonizes insulin action → decreased peripheral glucose uptake<br>• Promotes hepatic gluconeogenesis → elevated blood glucose<br>• Diabetogenic effect; chronic excess may induce insulin resistance |
| Lipid metabolism | • Stimulates lipolysis in adipose tissue<br>• Increases circulating free fatty acids<br>• Provides alternative energy substrate during fasting/energy deficit |
| Protein metabolism | • Promotes amino acid uptake in muscle<br>• Stimulates protein synthesis<br>• Supports tissue growth and repair |
| Clinical applications | • GH deficiency (restores growth, improves body composition)<br>• Metabolic disorders characterized by impaired growth<br>• Pediatric and adult populations |
| Therapeutic considerations | • Monitor for insulin resistance and hyperglycemia<br>• Balance benefits (muscle mass, reduced adiposity) against risks<br>• Cardiovascular effects require careful assessment |

and energy balance, with their actions being tissue-specific and context-dependent. Understanding these distinct effects is crucial for developing therapeutic strategies targeting metabolic disorders and growth deficiencies.

- Liver: GH and IGF-I are both essential for liver function, but they exert different effects. GH primarily stimulates the production of IGF-I in the liver, which is crucial for growth and development. However, IGF-I can also act independently of GH in the liver, influencing metabolic processes such as lipid metabolism and insulin sensitivity [44, 54]. In cases of adult GH deficiency, there is an increased prevalence of nonalcoholic fatty liver disease, suggesting that GH plays a protective role against liver fat accumulation [54].

- Adipose tissue: GH promotes lipolysis, leading to the breakdown of fat, whereas IGF-I has insulin-like effects that can enhance insulin sensitivity and potentially inhibit lipolysis [7, 55]. In studies with Zucker rats, a combination of GH and IGF-I reduced the relative weight of inguinal fat, although this effect was modest and site-specific [56]. The distinct roles of GH and IGF-I in adipose tissue metabolism highlight their potential as therapeutic targets for obesity management, with GH promoting fat breakdown and IGF-I enhancing insulin sensitivity [7].

- Skeletal muscle: GH and IGF-I both contribute to muscle growth and development, but they do so through different mechanisms. GH stimulates the production of IGF-I in muscle tissue, which acts in an autocrine/paracrine manner to promote muscle growth [44, 57]. In muscle-specific IGF-I receptor knockout models, the absence of IGF-I signaling led to severe insulin resistance, indicating the critical role of IGF-I in maintaining insulin sensitivity in muscle tissue [57].

- Pancreas: GH and IGF-I have opposing effects on the endocrine pancreas. GH increases pancreatic insulin and glucagon content, whereas IGF-I reduces serum insulin and C-peptide levels, suggesting an inhibition of insulin secretion [58]. Despite the reduction in insulin secretion by IGF-I, there is no resultant hyperglycemia, indicating enhanced insulin sensitivity, possibly due to IGF-I's insulin-like actions [58].

While GH and IGF-I have distinct roles in various tissues, their interplay is complex and context-dependent. For instance, in the liver, GH-induced IGF-I production is crucial for growth, but IGF-I can also act independently to influence metabolism. In adipose tissue, GH promotes lipolysis, whereas IGF-I enhances insulin sensitivity, highlighting their potential as therapeutic targets for metabolic disorders. Understanding these nuanced interactions is essential for developing effective treatments for conditions like obesity, diabetes, and growth deficiencies.

## Physiological Roles of IGF-I

IGF-I exerts its physiological effects primarily through binding to the IGF-I receptor, a tyrosine kinase receptor expressed in various tissues (Table 2) [59-68]. Upon ligand binding, IGF-I receptor undergoes autophosphorylation, activating downstream signaling pathways such as the PI3K-AKT and MAPK pathways, which promote cellular proliferation, differentiation, and survival [11]. These mechanisms facilitate tissue growth and development, particularly in skeletal and soft tissues. Unlike GH, which acts indirectly by stimulating IGF-I production, IGF-I can directly influence target cells, mediating many of its metabolic and anabolic effects [11]. The regulation of IGF-I activity is further modulated by IGF-binding proteins, which control its bioavailability and interaction with receptors, ensuring precise physiological responses [11].

**Table 2:** Summary of IGF-I physiological roles and clinical implications.

| Aspect | Key points |
|---|---|
| Primary mechanisms | • Binds to IGF-I receptor (tyrosine kinase family)<br>• Activates PI3K-AKT and MAPK signaling pathways<br>• Regulated by IGF-binding proteins controlling bioavailability<br>• Direct action on target cells (unlike GH's indirect effects) |
| Carbohydrate metabolism | • Enhances cellular glucose uptake and utilization<br>• Exerts insulin-like effects → maintains euglycemia<br>• Suppresses hepatic glucose production<br>• Improves insulin sensitivity (opposes GH's diabetogenic action) |
| Lipid metabolism | • Reduces lipolysis (opposes GH's lipolytic effects)<br>• Promotes lipid storage<br>• Associated with improvements in lipid profiles (↓ triglycerides, ↓ low-density lipoprotein) |
| Protein metabolism | • Promotes protein synthesis<br>• Stimulates cellular proliferation<br>• Contributes to tissue maintenance and repair<br>• Direct anabolic effects on muscle and other tissues |
| Clinical applications | • IGF-I deficiency states (e.g., severe growth failure)<br>• GH insensitivity syndromes (bypasses defective GH signaling)<br>• Insulin resistance and metabolic syndrome (insulin-sensitizing properties) |
| Therapeutic considerations | • Monitor for hypoglycemia (insulin-like effects)<br>• Risk of edema<br>• Careful dose titration required<br>• Potential benefits for glycemic control in insulin-resistant states |

IGF-I plays a significant role in modulating metabolic processes, often exerting effects that oppose those of GH. It promotes anabolic activities such as protein synthesis and cellular growth, contributing to tissue maintenance and repair [13]. In glucose metabolism, IGF-I enhances cellular glucose uptake and utilization, thereby exerting insulin-like effects that help maintain euglycemia [13]. Additionally, IGF-I influences lipid metabolism by reducing lipolysis and promoting lipid storage, which contrasts with GH's lipolytic actions [2]. These metabolic effects are crucial during growth and development but also have implications in metabolic disorders, where IGF-I's insulin-sensitizing properties may be beneficial. The suppressive effect of IGF-I on hepatic glucose production further underscores its role in maintaining metabolic homeostasis [13].

Clinically, recombinant IGF-I therapy is utilized in conditions characterized by IGF-I deficiency, such as severe growth failure and certain metabolic disorders. Its ability to promote growth and improve insulin sensitivity makes it a valuable therapeutic agent [13]. IGF-I therapy has shown promise in managing insulin resistance and metabolic syndromes, owing to its insulin-like effects on glucose and lipid metabolism [11]. Moreover, in patients with GH insensitivity syndromes, IGF-I administration can bypass defective GH signaling pathways, restoring growth and metabolic balance [13]. However, careful monitoring is essential due to potential adverse effects, including hypoglycemia and edema. Overall, IGF-I therapy exemplifies the clinical translation of its physiological roles, offering targeted treatment options for specific endocrine and metabolic conditions [13].

## Integrated Regulation of the GH-IGF-I Axis

The integrated regulation of the GH-IGF-I axis is a complex interplay of hormonal, metabolic, and physiological factors that influence growth, metabolism, and various bodily functions [69-77]. This axis involves GH and IGF-I, which are crucial for growth and development, as well as for maintaining metabolic homeostasis. The regulation of this axis is

influenced by factors such as exercise, nutrition, age, and disease states, which can alter the secretion and action of GH and IGF-I.

- Exercise and the GH-IGF-I axis: Physical activity is a significant stimulator of GH release, which in turn influences IGF-I production. Exercise-induced GH secretion is crucial for muscle growth and repair, particularly during adolescence when spontaneous physical activity levels are high [78, 79]. The anabolic effects of exercise on the GH-IGF-I axis are age-dependent, with a more pronounced impact during periods of rapid growth such as puberty [78]. GH replacement therapy has been shown to improve exercise capacity in GH-deficient individuals, although excessive GH levels do not enhance performance in healthy individuals [79].

- Metabolic regulation: The GH-IGF-I axis plays a vital role in lipid metabolism, influencing lipoprotein concentrations and cardiovascular health. GH deficiency and excess are both associated with increased cardiovascular risk [80, 81]. GH promotes lipolysis and lipid oxidation, while IGF-I has a more chronic effect on lipid metabolism. This axis is also involved in insulin resistance, with GH contributing to insulin resistance and IGF-I potentially ameliorating it [82].

- Physiological and pathological influences: The GH-IGF-I axis is regulated by various physiological factors, including age, obesity, and sleep. GH secretion declines with age and is inversely related to body mass index [83]. Gonadal hormones such as estradiol and testosterone enhance GH secretion, particularly during puberty [83]. In disease states, such as acromegaly and GH deficiency, the balance of GH and IGF-I is disrupted, leading to metabolic and cardiovascular complications [2, 81].

- Reproductive and developmental aspects: The GH-IGF-I axis is implicated in reproductive development, influencing the secretion of gonadotropin-releasing hormone and the onset of puberty [84]. IGF-I is essential for reproductive maturation and may enhance gonadal sensitivity to gonadotropins, although its precise role in the neuroendocrine regulation of reproduction requires further investigation [84].

While the GH-IGF-I axis is crucial for growth and metabolism, its regulation is subject to various influences that can alter its function. Factors such as intra-portal insulin levels, which affect hepatic GH sensitivity and IGF-I production, highlight the complexity of this regulatory system [2]. Understanding these interactions is essential for managing conditions related to GH and IGF-I imbalances, such as metabolic disorders and growth deficiencies.

## Comparative Analysis of Metabolic Effects

GH and IGF-I are central regulators of growth and metabolism, yet they exert contrasting effects on various metabolic pathways. GH primarily promotes lipolysis and antagonizes insulin action, leading to increased blood glucose levels, whereas IGF-I tends to enhance insulin sensitivity and promote anabolic processes [11]. Despite their interconnected roles within the GH/IGF axis, their divergent metabolic effects are well-recognized and form the basis for understanding their clinical implications [11].

GH exerts diabetogenic effects by stimulating hepatic gluconeogenesis and reducing peripheral glucose uptake, thereby elevating blood glucose levels [11]. This antagonistic action on insulin results in increased insulin resistance, which can predispose individuals to hyperglycemia, especially with chronic GH excess [13]. Conversely, IGF-I enhances insulin sensitivity by mimicking insulin's actions, promoting glucose uptake in muscle and adipose tissue, and suppressing hepatic glucose production [2]. These opposing effects are significant in clinical contexts, where GH excess may contribute to glucose intolerance, while IGF-I therapy can improve glycemic control in insulin-resistant states [14].

GH stimulates lipolysis in adipose tissue, leading to increased free fatty acids in circulation, which serve as alternative energy sources [12]. This lipolytic effect contributes to reductions in fat mass but may also elevate circulating free fatty acids, potentially impacting insulin sensitivity. In contrast, IGF-I has been associated with lipid profile improvements, including reductions in serum triglycerides and low-density lipoprotein cholesterol, partly through its insulin-sensitizing effects [41]. The opposing influences on lipid metabolism underscore the complex roles these hormones play in energy homeostasis and cardiovascular risk profiles.

Both GH and IGF-I promote anabolic effects on protein metabolism, but their mechanisms differ. GH stimulates amino acid uptake and protein synthesis indirectly by inducing IGF-I production in the liver and tissues [42]. IGF-I directly enhances protein synthesis and cellular proliferation, contributing to tissue growth and repair [43]. While both hormones support muscle anabolism, GH's effects are often mediated through IGF-I, and their combined actions are crucial for normal growth and maintenance. However, excessive GH can lead to disproportionate tissue growth and metabolic disturbances, whereas IGF-I's anabolic effects are more targeted and regulated [85].

This comparative analysis highlights the often-opposing roles of GH and IGF-I in metabolic regulation, emphasizing the importance of their balanced activity for maintaining metabolic health and informing clinical strategies for managing related disorders.

## Clinical Implications of Opposing Effects

The opposing metabolic effects of GH and IGF-I have significant implications for managing metabolic disorders. Given GH's propensity to elevate blood glucose levels and promote lipolysis, its therapeutic use must be carefully balanced to avoid exacerbating insulin resistance or hyperglycemia, particularly in patients with pre-existing metabolic syndromes [11]. Conversely, IGF-I's capacity to enhance insulin sensitivity and suppress hepatic glucose production suggests potential benefits in treating conditions characterized by insulin resistance, such as type 2 diabetes mellitus [13]. Understanding these divergent effects enables clinicians to tailor interventions that leverage the beneficial aspects of each hormone while mitigating adverse outcomes. For instance, in patients with metabolic syndrome, IGF-I therapy might be prioritized to improve glycemic control, whereas GH therapy could be cautiously employed in cases where lipid mobilization is desired without compromising glucose homeostasis [11].

In GH deficiency, the metabolic profile often includes increased fat mass, decreased lean body mass, and impaired glucose metabolism [12]. Administering GH can ameliorate these issues by promoting lipolysis and improving lipid profiles, but it may also induce hyperglycemia or insulin resistance if not carefully monitored [43]. Conversely, in GH excess, such as acromegaly, the metabolic effects include profound insulin resistance and dyslipidemia, driven by GH's antagonistic effects on insulin action [2]. The opposing actions of GH and IGF-I necessitate a nuanced approach: restoring GH levels in deficiency states can improve metabolic health, but excessive GH must be controlled to prevent metabolic derangements. Additionally, IGF-I therapy in GH

deficiency can help restore metabolic balance, but its effects on glucose metabolism must be considered to avoid hypoglycemia or other adverse effects [11].

Therapeutic modulation of GH and IGF-I offers potential benefits, such as improved growth, enhanced muscle mass, and better metabolic regulation. However, the opposing effects also pose risks. GH therapy may increase lipolysis and improve lipid profiles but at the expense of raising blood glucose levels, potentially precipitating diabetes or worsening existing glycemic control [14]. IGF-I therapy, while beneficial for insulin sensitivity, carries the risk of hypoglycemia and may influence lipoprotein levels adversely [13]. The balance between these hormones must be carefully managed to maximize benefits and minimize risks. Personalized treatment strategies, considering individual metabolic profiles and hormone sensitivities, are essential to optimize outcomes and prevent adverse effects associated with therapy [11].

## Clinical Studies

The metabolic effects of GH and IGF-I are complex and often opposing, particularly in their influence on glucose metabolism and insulin sensitivity. While GH is known to increase insulin resistance, IGF-I tends to enhance insulin sensitivity, creating a dynamic interplay that is crucial for understanding their roles in metabolic regulation. This dichotomy is evident in various clinical studies and has significant implications for treatment strategies in conditions like GH deficiency and diabetes.

A study by Lu et al. [86], a secondary analysis of the TODAY trial (NCT00081328), investigated the associations of GH mediators with glycemic failure, beta cell function, and insulin sensitivity in youths with type 2 diabetes (Figure 1). The analysis included 398 participants, with a mean age of 13.9 years, predominantly girls (62%), and a diverse ethnic representation. A greater increase in IGF-1 levels between baseline and 36 months was significantly associated with a lower likelihood of glycemic failure. Specifically, for every 100-ng/mL increase in IGF-1, the odds ratio (OR) for glycemic failure was 0.995 (95% confidence interval (CI): 0.991 to 0.997; $p < 0.001$). An increase in IGF-1 was also linked to improved beta cell function, as indicated by a higher C-peptide index. The beta coefficient (β) was 0.015 (Standard error (SE), 0.003; $p < 0.001$) per 100-ng/mL increase in IGF-1. A greater increase in the log2 GH receptor level from baseline to 36 months was associated with a higher probability of glycemic failure. The OR was 1.75 (95% CI: 1.05 to 2.99; $p = 0.04$). This increase in log2 GH receptor was also associated with reduced beta cell function, indicated by a lower C-peptide index. The β was −0.02 (SE, 0.006; $p < 0.001$). A greater increase in the log2 IGF binding protein 1 level between baseline and 36 months was associated with a higher odd of glycemic failure. The OR was 1.37 (95% CI: 1.09 to 1.74; $p = 0.007$). An increase in log2 IGF binding protein 1 was also associated with higher high-molecular-weight adiponectin levels. The β was 431 (SE, 156; $p = 0.007$). In summary, the study indicates that changes in plasma GH mediators are significantly associated with the loss of glycemic control in youth-onset type 2 diabetes. Specifically, an increase in IGF-1 is linked to a lower risk of glycemic failure and better beta cell function, while increases in GH receptor and IGF binding protein 1 are associated with an increased risk of glycemic failure and altered metabolic markers.

A study by Nazari et al. [87] investigated the effects of a 16-week concurrent resistance-aerobic training program on various physiological markers in children with type 1 diabetes (IRCT20150531022498N30). The exercise training intervention led to a significant reduction in the fasting blood sugar index ($p = 0.002$). A significant decrease in glycosylated hemoglobin (HbA1c) was also observed ($p = 0.003$). GH levels significantly increased, but this effect was noted only in the experimental group ($p = 0.037$). No significant difference was found in IGF-1 levels ($p = 0.712$). Interleukin-1β levels did not change significantly in either the experimental or control group when compared to pre-test measurements ($p > 0.05$). Similarly, high-sensitivity C-reactive protein levels showed no significant change in either group compared to pre-test ($p > 0.05$). In conclusion, the concurrent resistance-aerobic training program demonstrated positive effects on blood glucose control and GH levels in children with type 1 diabetes, suggesting that moderate-intensity exercise can be beneficial for this population. However, it did not significantly impact the measured inflammatory markers or IGF-1.

A study by AbdlWhab et al. [88] investigated the impact of insulin resistance and glycemic control on IGF-1 levels in patients with type 2 diabetes mellitus (Figure 2). Patients with poorly controlled diabetes, defined as an HbA1c > 8, showed significantly elevated IGF-1 levels. Their mean IGF-1 was 166 compared to 134 in those with HbA1c < 8, with a statistically significant difference ($p = 0.016$). Patients exhibiting insulin resistance had significantly lower mean IGF-1 levels (143) compared to those without insulin resistance (192), a difference that was statistically significant ($p = 0.001$). A significant negative

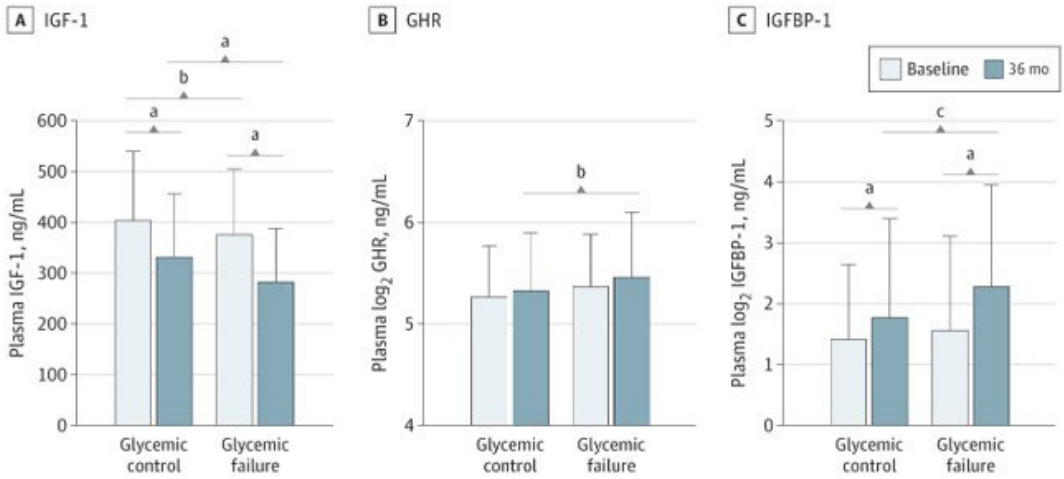



**Figure 1:** Baseline and 36-month changes in GH axis mediators relative to glycemic outcomes in the treatment options for type 2 diabetes in adolescents and youth study [86].

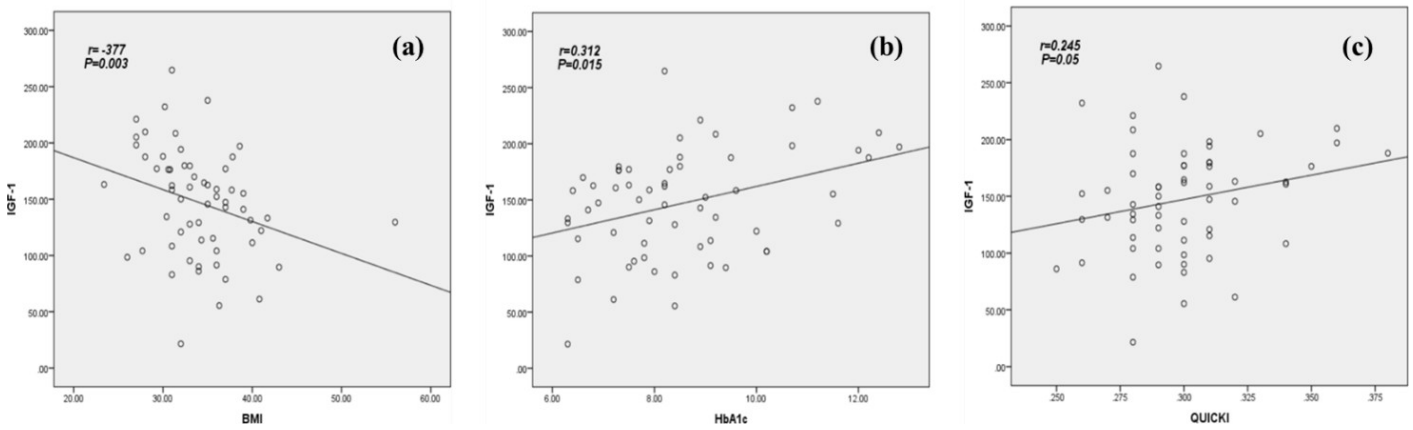



**Figure 2:** Spearman's rank correlation coefficients were calculated to evaluate the relationships between IGF-1 concentrations and 3 diabetes-related factors: **(a)** body mass index, **(b)** HbA1c, and **(c)** QUICKI [88].

correlation was observed between IGF-1 levels and body mass index. IGF-1 levels showed a significant positive correlation with HbA1c and the Quantitative Insulin Sensitivity Index (QUICKI). Elevated IGF-1 levels were observed to increase with advancing age, longer duration of type 2 diabetes mellitus, higher HbA1c, higher QUICKI, and lower body mass index. No significant differences were found in IGF-1 values concerning Homeostatic Model Assessment of Beta-cell function (HOMA-β), fasting insulin, and waist-hip ratio. In summary, the study found that poorly controlled type 2 diabetes mellitus is associated with higher IGF-1 levels, while insulin resistance and obesity (indicated by higher body mass index) are linked to lower IGF-1 levels. IGF-1 also correlated positively with age, diabetes duration, HbA1c, and QUICKI, and negatively with body mass index.

A study by Lin et al. [89] investigated the effects of Metformin + SGLT2i and Metformin alone on various blood indices and the GH/IGF1 axis in newly diagnosed male type 2 diabetes patients over 12 weeks. After 12 weeks, patients treated with Metformin + SGLT2i showed significant improvements in fasting plasma glucose, HbA1c, Homeostatic Model Assessment of Insulin Resistance (HOMA-IR), HOMA-β, and urinary albumin-to-creatinine ratio ($p < 0.05$). IGF-1 levels significantly increased ($p = 0.01$). The IGF-1/IGF binding protein 3 ratio significantly increased ($p < 0.01$). GH and IGF binding protein 3 levels did not change significantly. The metformin group experienced reductions in fasting plasma glucose and HbA1c levels. Metformin alone did not significantly affect IGF-1, IGF-1/IGF bind protein 3 ratio, GH, IGF binding protein 3, or HOMA-IR. SGLT2i significantly improved HOMA-IR levels ($p = 0.04$) when compared to the metformin group. SGLT2i also significantly elevated the IGF1/IGF binding protein 3 ratio ($p = 0.04$). There was no significant difference between the groups regarding GH, IGF-1, and IGF binding protein 3 levels. Blood IGF-1 levels were found to be negatively correlated with fasting plasma glucose, HbA1c, and HOMA-IR. Conversely, IGF-1 was positively correlated with IGF binding protein 3. Regression analysis indicated that fasting plasma glucose and testosterone had a negative effect on blood IGF-1 levels, while HOMA-IR did not show an obvious effect on blood IGF-1. In summary, the study concluded that SGLT2i treatment in newly diagnosed male type 2 diabetes patients effectively increases the IGF-1/IGF binding protein 3 ratio and alleviates insulin resistance, despite not significantly altering GH and IGF-1 levels directly. The observed increase in blood IGF-1 and improved insulin resistance following metformin + SGLT2i treatment suggests a beneficial role for IGF-1 in this patient population.

A study by Jensterle et al. [90] evaluated the efficacy of somapacitan in adult patients with GH deficiency who experienced fatigue from daily GH injections. The findings highlight somapacitan's convenience and comparable effectiveness to daily GH in several key areas, with some notable differences in bone mineral density (Figure 3). Somapacitan was found to be significantly more convenient than daily GH, with a notable difference in the Treatment Satisfaction Questionnaire for Medication-9 (TSQM-9) score for convenience, favoring somapacitan. This improvement was particularly pronounced in patients with childhood-onset GH deficiency, suggesting that a longer history of GH therapy might lead to a greater perceived benefit from switching to a once-weekly regimen. Patients switching to somapacitan reported better self-reported adherence compared to those continuing daily GH. In the month before inclusion, fewer somapacitan patients missed doses compared to daily GH patients. Somapacitan was effective in maintaining IGF-1 levels, comparable to daily GH. The mean IGF-1 levels and IGF-1 standard deviation score were maintained from baseline to study end in both treatment arms, with similar values between the groups. The improvements in adipose tissue and lean body mass achieved with pre-trial GH treatment were maintained, with no statistically significant differences observed between treatment arms for these endpoints. There was a significant difference in the bone mineral density of the lumbar spine, favoring daily GH, with somapacitan showing a non-significant decrease. Specifically, the estimated difference for lumbar spine bone mineral density was −0.036 (95% CI: −0.064 to −0.009) g/cm$^2$, with a p-value of 0.011. Significant differences were also observed in bone mineral content, with an estimated difference of −3.661 (95% CI: −6.909 to −0.413) g, favoring daily GH. No significant differences were observed between treatment arms in estimated changes from baseline to study end for IGF-1 levels, glucose and lipid parameters. Fasting plasma glucose or HbA1c showed no clinically relevant changes. Somapacitan maintained vascular parameters, such as carotid intima media thickness and reactive hyperemia index, comparably to daily GH, with no significant differences in estimated change from baseline. In summary, the study concluded that somapacitan offers a more convenient treatment option for adult GH deficiency patients fatigued by daily GH injections, maintaining IGF-1 levels and body composition similar to daily GH. While generally comparable across many parameters, a notable difference was observed in lumbar spine bone mineral density and bone mineral content, favoring daily GH.

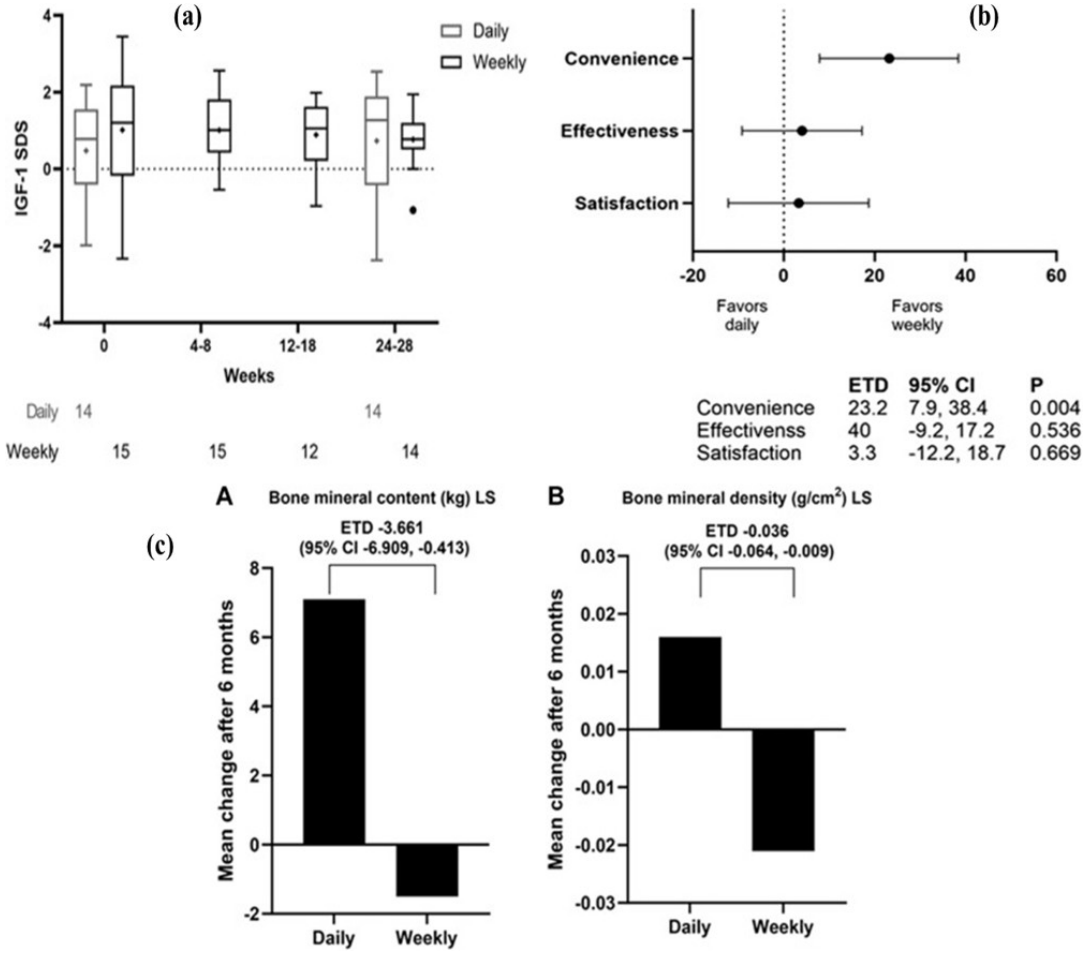



**Figure 3: (a)** Distribution of IGF-1 standard deviation scores across multiple time points by treatment regimen (daily: grey; weekly: black). **(b)** Estimated treatment difference at 6 months for TSQM-9 score change, weekly versus daily treatment. **(c)** Estimated treatment difference for 6-month changes in lumbar spine bone parameters (bone mineral content and density), weekly versus daily regimens [90].

## Future Directions in Research

Despite substantial progress in elucidating the opposing metabolic effects of GH and IGF-I, significant gaps remain that warrant further investigation. Current understanding is primarily based on mechanistic insights and clinical observations, yet the complex interplay between these hormones across different physiological and pathological states is not fully characterized [11]. Future research should focus on delineating the molecular pathways that mediate their divergent actions, particularly in diverse tissue types and disease contexts. Additionally, longitudinal studies are needed to assess the long-term metabolic consequences of modulating GH and IGF-I levels, especially in populations with metabolic disorders or hormonal imbalances [11]. Advancing assay technologies and biomarker identification will also be crucial for more precise assessment of hormonal activity and metabolic outcomes, as highlighted by recent developments in biochemical measurement techniques [41]. Addressing these gaps will enhance our understanding of the nuanced roles of GH and IGF-I and inform more targeted therapeutic strategies.

The recognition of opposing metabolic effects opens avenues for innovative therapeutic interventions that selectively harness or inhibit specific pathways mediated by GH and IGF-I. For instance, modulating GH activity could be beneficial in conditions characterized by insulin resistance or dyslipidemia, whereas enhancing IGF-I signaling might improve anabolic states without adverse metabolic effects [11]. Emerging research suggests that targeting downstream signaling components or receptor sensitivities could allow for more precise control over metabolic outcomes, minimizing side effects associated with broad hormone modulation [13]. Furthermore, understanding the differential effects on glucose, lipid, and protein metabolism provides a foundation for developing hormone analogs or antagonists tailored to individual metabolic profiles. Such approaches could revolutionize treatment paradigms for metabolic syndromes, growth disorders, and age-related decline, emphasizing the importance of continued research into the distinct and overlapping pathways of GH and IGF-I [2].

Given the complex and sometimes opposing effects of GH and IGF-I, combination therapies that strategically modulate both hormones hold promise for optimizing metabolic health. Preliminary studies indicate that concurrent or sequential administration of GH and IGF-I can produce synergistic or balanced effects, potentially mitigating adverse outcomes associated with monotherapy [14]. For example, combining GH with IGF-I analogs or receptor modulators could enhance anabolic effects while controlling hyperglycemia or dyslipidemia. Moreover, personalized medicine approaches, integrating genetic, biochemical, and clinical data, could identify patient subsets most likely to benefit from such combination strategies [42]. Future research should focus on

designing clinical trials to evaluate the safety, efficacy, and long-term outcomes of combination therapies, as well as elucidating the optimal dosing regimens and timing to maximize benefits and minimize risks [43]. This exploration could lead to more refined and effective interventions for a range of metabolic and growth-related conditions.

## Conclusion

The review underscored the complex and often opposing metabolic effects of GH and IGF-I. Despite their interconnected roles within the GH-IGF axis, GH predominantly exerts catabolic effects on glucose and lipid metabolism, often leading to insulin resistance and increased lipolysis, whereas IGF-I generally promotes anabolic processes, enhancing insulin sensitivity and lipid storage. These divergent actions are rooted in their distinct mechanisms of action and tissue-specific responses, which have significant implications for clinical practice. Understanding these opposing effects is crucial for optimizing therapeutic strategies, particularly in managing metabolic disorders and growth deficiencies, where careful modulation of GH and IGF-I levels can mitigate adverse outcomes.

Clinically, the opposing metabolic effects of GH and IGF-I necessitate a approach to therapy. For instance, GH therapy, while beneficial in GH deficiency, must be carefully balanced to avoid exacerbating insulin resistance or dyslipidemia. Conversely, IGF-I therapy offers potential benefits in improving insulin sensitivity and metabolic profiles but carries risks such as hypoglycemia and lipoprotein alterations. These contrasting effects highlight the importance of personalized treatment plans that consider the patient's metabolic status and underlying conditions. Future research should focus on elucidating the precise mechanisms governing these effects and exploring combination therapies that leverage their beneficial aspects while minimizing risks. Ultimately, a deeper understanding of the opposing actions of GH and IGF-I will enhance clinical outcomes and facilitate the development of targeted interventions for metabolic and growth-related disorders.

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## Conflict of Interest

None.

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